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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/584,766	BEISSERT ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-74* is/are pending in the application.

4a) Of the above claim(s) *27-32,45-50 and 60-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-26,33-44,51-59 and 72-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of record has changed. Please direct all further correspondence to Scott Long whose phone number is 571-272-9048.

Election/Restrictions

Examiner acknowledges the election, with traverse, of Group I directed to a method for stimulating hair growth by administering a polynucleotide comprising SEQ ID NO:1, in the reply filed on 2 December 2008. Additionally, the applicant elected, with traverse, the species, saponins.

The applicant has traversed the restriction requirement on two bases: (1) there is a special technical feature "when taken as a whole" links all of the groups as a single inventive entity and (2) there is no serious search burden.

The current examiner agrees with the previous examiner's need for a Restriction and disagrees with the applicant's traversal for the following reasons:

The inventions listed as Groups I-IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions are drawn to multiple methods and multiple products, therefore as per 37 CFR § 1.475(a)-(d), applications containing claims drawn to more than one categories of invention (as

defined by section (b)) are not considered to have unity of invention (see particularly section (c)). See the following:

> 37 CFR § 1.475 Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage.
>
> (a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
>
> **(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:**
>
> **(1) A product and a process specially adapted for the manufacture of said product; or**
> **(2) A product and process of use of said product; or**
> **(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or**
> **(4) A process and an apparatus or means specifically designed for carrying out the said process; or**
> **(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.**
>
> **(c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.**
>
> (d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).

In the instant case, the claims are do not meet the requirements of paragraph (b). There are numerous methods which are directed to stimulating hair growth, but which use chemically distinct compounds to treat hair loss, such as nucleic acids (Group I), polypeptides (Group III), an unspecified compound which binds to an antibody (Group V) and a compound which specifically binds to an IL-15 receptor alpha (Group VI).

None of these methods share the same reagents and therefore are distinct. In addition, the claims are directed to a transgenic animal comprising SEQ ID NO:1 (Group VIII) which is not used in any of the recited methods, nor is the transgenic animal made by any of the recited methods. Because the various groups do not fit into the prescribed categories indicated as having unity of invention, the examiner finds them to lack unity of invention. Furthermore, the examiner finds that each of these groups would be an undue burden to search because numerous different databases would need to be searched using non-overlapping queries; for example, a search for methods using polynucleotide SEQ ID NO:1 would not overlap with methods using compounds which bind to IL-15 alpha. Additionally, searching for a transgenic animal would require a different search query from methods for stimulating hair growth, even if they both encompass the use of SEQ ID NO:1. Therefore, the examiner finds the applicant's traversal unpersuasive.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claim Status

Claims 24-71 are pending. However, claims 27-32, 45-50, and 60-71 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-23 are cancelled. Claims 24-26, 33-44, 51-59 and 72-74 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. The examiner was not able to identify a statement that the Computer Readable Form (CRF) and the Sequence Listing are identical. The applicant should submit a statement that both CRF and the Sequence Listing are identical.

In addition, the examiner notes that the CRF and Sequence Listing were submitted on 13 August 2007, which is more than a year after filing the instant National Stage Application (28 June 2006). After reviewing the priority document, PCT/EP04/013907, it seems that the Sequence Listing for the International Application was received on 3 July 2006, after the filing of the instant US National Stage Application. Therefore, while the examiner concludes that the instant application is not entitled to a benefit date from the International Application PCT/EP04/013907.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 15 March 2007 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 11 January 2007 consisting of 4 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from International U.S. Application No. PCT/EP04/13907, filed 7 December 2004 and Foreign Application, EPO 03029899.6 (filed 29 December 2003).

The examiner notes that the CRF and Sequence Listing were submitted on 13 August 2007, which is more than a year after filing the instant National Stage Application (28 June 2006). After reviewing the priority document, PCT/EP04/013907, it seems that the Sequence Listing for the International Application was received on 3 July 2006, shortly after the filing of the instant US National Stage Application. Because the applicant is required to submit a complete copy of the international application including the sequence listing, the Examiner cannot extend benefit of the Sequence Listing to the Foreign Application or International Application.

Therefore, claims reciting SEQ ID NOs of the instant application have been granted the benefit date, 13 August 2007, from the submission of the instant Sequence Listing and CRF.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

Claims 24-26, 33-44, 51-59 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims encompass a genus of nucleic acids having at homology to SEQ ID NO:1 (or nucleic acids encoding amino acid sequence SEQ ID NO:2) and having hair growth activity. Particularly, claim 24 is directed to a method for stimulating hair growth comprising administering to a subject in a therapeutically effective amount of a composition comprising: (i) a polynucleotide comprising (a) a nucleic acid sequence as shown in SEQ ID NO:1; (b) a nucleic acid sequence encoding an amino acid sequence as shown in SEQ ID NO:2; (c) a nucleic acid sequence encoding an amino acid sequence as shown in SEQ ID NO:2 having a modified signal peptide, a modified N-terminus and/or a modified C-terminus, or (d) a nucleic acid sequence which hybridizes under stringent conditions to any one of (a) to (c).

Under the new Written Description Guidelines (March 25, 2008, Revision 1) the examiner is directed to determine whether one skilled in the art would recognize that the

applicant was in possession of the claimed invention as a whole at the time of filing. The following considerations are critical to this determination:

a. Actual Reduction to Practice. In the instant case, the specification shows an embodiment, SEQ ID NO:1 (polynucleotide) and SEQ ID NO:2 (polypeptide) which are reduced to practice.

b. Disclosure of structure. The applicant has provided sequence listings of SEQ ID NO:1 (DNA) and SEQ ID NO:2 (RNA). Additionally, with the help of a computer, a skilled artisan could identify all nucleic acids which could encode the full length sequence of SEQ ID NO:2. However, neither the specification nor the art indicate a relationship between the structure of the claimed genus of nucleic acids and the recited hair growth activity. In particular, there is no indication in the art or specification as to the effect of varying the N-terminus or C-terminus or the large genus of polynucleotides encompassed by claim 24-d on the hair growth function of the nucleic acids that are not 100% identical to SEQ ID NO:1 (or the polypeptide SEQ ID NO:2).

The instant claims are broadly drawn, such that they apply a genus of nucleic acid that hybridizes under high stringency to SEQ ID NO:1. The specification does not demonstrate any examples of nucleic acids that hybridize in to SEQ ID NO:1. With respect to claims limiting a polynucleotide by hybridization conditions, even under relatively high stringent conditions, the claimed nucleotide sequence could hybridize to a genus of polynucleotides that are similar, but not identical to the recited polynucleotides. The limitation by hybridization is obviously generic to a considerable number of nucleotides varying in the length of the nucleic acids, the degree of

homologies among the sequences, and the biological activities of the encoded polypeptides, which may or may not be involved in the function of hair growth. This genus also embraces sub-sequences that are unknown and include unsequenced polynucleotides, whose function is yet to be determined.

c. Sufficient relevant identifying characteristics. As mentioned in "b" above, the complete sequence of SEQ ID NO:1-2 are provided. In the context of a transgenic mouse, these sequences demonstrate hair growth activity. However, the new written description guidelines indicate in Examples 10 and 11A that without disclosure about which nucleotides can vary from SEQ ID NO:1 or 2 and still retain the claimed activity, the examiner should conclude that the applicant was not in possession of the claimed genus of isolated nucleic acids based on disclosure of the single species of SEQ ID NO:1 or 2.

d. The method of making the claimed invention is not well established. Producing the large genus of polynucleotides is possible, but would require

e. The level of skill in the art is high, with numerous researchers in the field of gene therapy having education at the PhD or MD level.

f. However, the art of gene therapy to skin (an in particular for treating alopecia) is not very predictable to a skilled artisan. Generating the genus of nucleic acid sequences is well within the ability of a skilled artisan. However, predicting which nucleotides can be varied from SEQ ID NO:1 or 2 and still retain hair growth activity would be unpredictable, based on the state of the art and the instant application.

Therefore, the examiner concludes that there is insufficient written description of the instantly claimed genus.

LACK OF ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-26, 33-44, 51-59 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2)

the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

NATURE OF THE INVENTION

The breadth of the claims encompasses gene therapy methods of stimulating hair growth by administering a polynucleotide comprising SEQ ID NO:1.

In addition, the scope of the claims encompasses a large genus of polynucleotides having hair growth activity. The full scope of the claimed invention encompasses an enormous number of nucleic acids which could hybridize with SEQ ID NO:1. The size of these hybridizing nucleic acids might be small, or equal in size to full-length SEQ ID NO:1, or larger than SEQ ID NO:1. The nucleic acids might also encompass very large nucleic acids that hybridize under highly stringent conditions only over a short range near one end of both sequences. In this case, there would be a very low level of homology between the two sequences, despite high stringency hybridization.

With respect to claims limiting a polynucleotide by hybridization conditions, even under relatively high stringent conditions, the claimed nucleotide sequence could hybridize to a genus of polynucleotides that are similar, but not identical to the recited polynucleotides. The limitation by hybridization is obviously generic to a considerable

number of nucleotides varying in the length of the nucleic acids, the degree of homologies among the sequences, and the biological activities of the encoded polypeptides, which may or may not be involved in hair growth. This genus also embraces sub-sequences that are unknown and include unsequenced polynucleotides, whose function is yet to be determined.

GUIDANCE & WORKING EXAMPLES

The specification does not provide guidance for or a working example for gene therapy methods of stimulating hair growth by administering a polynucleotide comprising SEQ ID NO:1, as required by claim 1. In addition, the specification does not provide guidance for or a working example for gene therapy methods of treating, preventing and/or ameliorating hair loss by administering a polynucleotide comprising SEQ ID NO:1, as required by claim 42. Furthermore, the specification does not provide guidance for or a working example for gene therapy methods of manufacturing non-human animal hair by administering a polynucleotide comprising SEQ ID NO:1, as required by claim 72. The absence of working examples directed to these gene therapy methods necessitates further experimentation. Therefore, the specification does not provide sufficient guidance on how to make and use the instantly claimed methods.

Much of the instant specification is directed to a transgenic mouse which overexpresses IL-15. Writing about the transgenic mice, the specification states "[i]n

this context it should be emphasized that IL-15 will not merely prevent apoptosis but also stimulate and promote growth of the cells" (page 10, lines 19-20). When every cell in the animal overexpresses IL-15, the applicants seem able to restimulate growth of keratinocytes at the site of hair follicles. However, this type of systemic expression will not be present in a gene therapy approach. The transgenic mouse is not an adequate equivalent for topically delivered gene therapy methods.

Regarding the scope of the polynucleotide sequences, there are no working examples of nucleic acids that have been isolated through the stringent hybridization method.

STATE OF THE ART & QUANTITY OF EXPERIMENTATION

The nature of the invention being gene therapy, the state of the prior art is not well developed and is highly unpredictable. Verma et al (Nat. 1997 Sep; 389:239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Phar Basis Ther 1995; 77-101) explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the

stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. (paragraph bridging pages 81-82) Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3).

Specifically, Danilenko et al. (Molecular Medicine Today. November 1996; pages 460-467) indicates the state of the art regarding stimulating hair growth by topical gene therapy methods is not well developed and poses the question, "can genes encoding growth factors or cytokines be delivered topically such that sustained and therapeutic levels of protein are produced locally within or near hair follicles?" (page 466, last sentence). In addition, Danilenko et al. teach "In the realm of topical delivery alone, further research into and development of new formulation for the delivery of proteins and genes will be necessary before the safe, effective and sustained delivery of growth factors or cytokines to hair follicles for the treatment or prevention of alopecia becomes a reality." (page 467, last sentence).

A skilled artisan would not know how to make a nucleic acid which corresponds to the large number of species of nucleic acid encompassed by Claims 1, 42, and 72. Some of the nucleic acids that fit within the genus would not be homologues of SEQ ID NO:1. In fact, despite hybridizing under high stringency conditions, these molecules would be structurally and functionally unrelated to SEQ ID NO:1-2. Sequences which fit into this class of unrelated molecules would require further research in order for an

artisan to learn how to use them. Furthermore, the artisan would have no reason to make such sequences.

Wolcott (CLINICAL MICROBIOLOGY REVIEWS, Oct. 1992, p. 370-386) teaches "hybridization…is subject to…nonspecific background interference" (page 372, column 1) and "hybridization studies…produced…false-positive reactions" (page 371, column 2). Walcott further teaches "short probes…are subject to more nonspecific hybridizations, are limited in specificity, and are more difficult to label….Long probes hybridize more stably than short probes at high temperatures and low salt concentrations (low stringency)." (page 371, column 2). Gress et al. (*Mammalian Genome 3:* 609-619, 1992) teach, "complex probes usually generate a high amount of background and unspecific hybridization." (page 610, column 1). The teachings of Wolcott and Gress et al. cast doubt on the homology of the sequences derived through hybridization methods. If sequences that hybridize under stringent conditions are not homologous or functionally related to those sequences of the genus of claim 7, then there is surely difficulty for the artisan to make and/or use these sequences. Or if the amount of relatedness of the hybridizing sequence to SEQ ID NO:1 is only comprises a single domain, then the artisan would likewise encounter difficulty in using these sequences and would be required to perform further investigation to find a utility for these discovered sequences.

CONCLUSION

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require undue experimentation to practice the invention.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633